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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/300,959	04/27/1999	MAURIZIO ZANETTI	P-ZA-3519	5037

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EXAMINER
WEHBE, ANNE MARIE SABRINA

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/300,959	Applicant(s) Zanetti
	Examiner Anne Marie Wehbé	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 18, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-29 and 31-37* is/are pending in the application.

4a) Of the above, claim(s) *1, 2, 5-17, 22-28, and 33* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *3, 4, 18-21, 29, 31, 32, and 34-37* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *19*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicant's amendment received on 11/18/02 has been entered. New claims 36-37 have been added. Claims 1-29, and 31-37 are pending in the instant application. Of these, claims 1-2, 5-17, 22-28 and 33 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. A complete reply to this final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 3-4, 18-21, 29, 31-32, and 34-37 are currently under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in the previous office actions.

Claim Rejections - 35 USC § 112

The rejection of claims 3-4, 18-21, 29, 31-32, and 34-37 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained in part. Applicant's arguments and the declarations under 37 C.F.R. 1.132 by Maurizio Zanetti have been fully considered but have not

been found persuasive in overcoming the following instant grounds of rejection for reasons of record as discussed in detail below.

Based on the evidence provided in the declaration under 37 C.F.R. 1.132 by Maurizio Zanetti the following subject matter has been found to be enabled by the specification: methods of stimulating an immune response and methods of treating a condition in a mammal comprising the intrasplenic injection of a DNA plasmid comprising a nucleic acid encoding a heterologous polypeptide antigen operably linked to a B cell expression element, wherein the expression of said heterologous polypeptide antigen in B cells results in the stimulation of an immune response against said antigen.

Please note that the applicant has overcome the previous grounds of rejection concerning B cell expression elements other than the immunoglobulin heavy chain promoter/enhancer by reference to Maxwell et al. which teaches that the kappa-light chain promoter and enhancer were also known in the art prior to applicant's filing date.

In regards to the lack of enablement for using any type of nucleic acid in the disclosed methods, the applicant argues that the art recognized unpredictability of utilizing various types of expression vectors and different promoter for expressing therapeutic amounts of a gene *in vivo* as evidenced by Verma et al., Eck et al., Deonarian et al., and Miller et al., is not relevant to the instant claims because the claims recite that the epitopes are expressed in a B cell. The fact that applicants have claimed a particular limitation does not establish that the specification provides an enabling disclosure for the claimed limitation and subject matter. The applicant is reminded that

the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Further, in patentability context, claims are to be given their broadest reasonable interpretations, and limitations are not to be read into the claims from the specification. *In re Van Guens*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The office has analyzed the teachings of the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. Please note as well that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of a broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991).

As discussed in detail in previous office actions, the specification's working examples are limited to the use of DNA plasmid vectors which utilize the immunoglobulin heavy chain promoter/enhancer. The applicant has not provided any compelling evidence or arguments that the skilled artisan at the time of filing would consider the use of any nucleic acid other than a plasmid DNA as predictable in applicant's methods. Based on the evidence of record (Verma et al., Eck et al., Deonarian et al., and Miller et al.) which teaches the unpredictability of vector and promoter selection for achieving therapeutic levels of gene expression in target cells *in vivo*, applicant's working examples and declaratory evidence, exhibit B, which are limited to the use of

DNA plasmid vectors do not provide sufficient enablement for applicant's broad claims. The applicant is reminded that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991).

In regards to routes of immunization other than intrasplenic injection and the unpredictability of targeting B cells in vivo, the applicant argues that the specification identifies other target tissues, such as lymph nodes. However, as previously noted, the cellular composition of the spleen versus gut associated lymph organs, or lymph nodes is very different in terms of the percentages of different antigen presenting cells and the types of antigen presenting cells present. Although the specification and declaratory data, exhibit B, demonstrates that direct injection of the spleen results in the generation of immune responses, the specification fails to provide any evidence that the administration of the nucleic acids to any other lymphoid tissue would result in comparable levels of antibody or T cell mediated responses. While the office acknowledges the comments made in the declaration by Maurizio Zanetti, exhibit A, that the spleen and other lymph tissue share some common properties, the declaration fails to provide concrete evidence that the level of B cells in the spleen versus peripheral lymph nodes is equivalent or that B cells present in a peripheral lymph node are capable of stimulating therapeutic immune responses following direct injection of a plasmid or other nucleic acid to the lymph node.

Further, while claims 3-4, 18-21, and 34 are limited to the administration of the vector to lymphoid tissue, claims 29-32 are not so limited and broadly read on the administration of the

nucleic acid by any route of administration. The applicant argues that the articles cited to support the unpredictability of targeting a vector to a particular cell type *in vivo* are not applicable to the instant claims since the claims recite that the polypeptide antigens are expressed in a B cell. However, as discussed in detail in previous office actions, the specification fails to provide an enabling disclosure for targeting B cells using any route of administration. Further, the cited articles, particularly Deonarian and Miller, clearly teaches that specific targeting of a nucleic acid to a particular cell was unpredictable at the time of filing. For example, Deonarain teaches that one of the main obstacles to successful gene therapy is, " ... the ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time", and states that, " .. even after almost 30 years of relentless pursuit, nothing has yet delivered such a promise in terms of clinical results" (Deonarain et al., page 53, lines 1-4, and page 54, lines 12-15). Miller et al. concurs, teaching that the development of surface targeting has been problematic and that the biggest challenge in targeted vector design is to combine targeting with efficiency of gene expression, since , " attainment of one usually compromises the other" (Miller et al., page 198, paragraph 2). The specification does not provide guidance in the form of detailed teachings or specific working examples for methods to target any vector to B cells *in vivo* or *in vitro*. Therefore, in view of the art recognized unpredictability of targeted gene expression *in vivo*, the lack of guidance provided by the specification for vectors suitable for specifically targeting B cells, the lack of working examples concerning methods of targeted delivery other than

intrasplenic injection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 34 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of applicant's amendments to claim 34.

Claim 19 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 19 depends on claim 18. Claim 18 has been amended to recite the limitation that the expression element is a B cell expression element. Thus, claim 19 is confusing in that it states that the expression element functions in B cells, T cells, or dendritic cells. Clarification is requested.

Claim 20 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 20 depends on claim 18. Claim 18 has been amended to recite that the nucleic acid sequence encodes a heterologous polypeptide antigen. Claim 20 refers to a

polypeptide. Based on the amendment to claim 18, the term polypeptide lacks antecedent basis. It is suggested that claim 20 be amended to recite "a polypeptide antigen".

Claim Rejections - 35 USC § 102

The rejection of claims 18-19 under 35 U.S.C. 102(b) as being anticipated by Maxwell et al. is withdrawn in view of applicant's amendments to claim 18 which now recite that the polypeptide is an antigen that functions as a vaccine.

Claim Rejections - 35 USC § 103

The rejection of claims 3-4, 29, 31, and 35 under 35 U.S.C. 103 over Hurpin et al. in view of Banerji et al. is maintained and extended to include amended claims 18-19. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that neither Hurpin et al. nor Banerji et al. provides sufficient motivation for modifying the vector taught by Hurpin et al. to include B cell specific expression elements. The applicant further argues that no specific suggestion is found in Hurpin to target B cells in the spleen, and that no specific suggestion is found in Banerji to express heterologous epitopes in B cells.

As stated in the previous office action, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or **in the knowledge generally available to one of ordinary skill in the art**. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Banerji et al. supplements Hurpin et al. by teaching a plasmid encoding the β-globin gene operatively linked to the immunoglobulin enhancer which is a B cell specific expression element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Banerji et al. further provides motivation for using a B cell specific enhancer by teaching that use of the immunoglobulin heavy chain enhancer to express a heterologous gene, β-globin, results in two fold increase in the magnitude of β-globin expression compared to vectors which utilize the viral SV40 enhancer (Banerji et al., page 729, abstract). Please note that β-globin is a heterologous epitope. Thus, based on the increased magnitude of gene expression using the immunoglobulin promoter as taught by Banerji et al., and the large percentage of B cells in the spleen, it would have been *prima facie* obvious at the time of filing to substitute the immunoglobulin heavy chain transcriptional elements taught by Banerji et al. for the viral elements taught by Hurpin et al. in order to increase antigen expression in the spleen and thus increase resulting immune responses. Based on the successful generation of immune responses observed by Hurpin et al. using intrasplenic injection, and the activity of the immunoglobulin promoter observed by Banerji, the

skilled artisan would have had a reasonable expectation of success in using the immunoglobulin heavy chain promoter/enhancer in the vectors and methods taught by Hurpin et al.

The fact that Hurpin et al. teaches that immune responses can be generated using viral expression elements does not contraindicate the use of an alternate expression element that has been demonstrated to be more potent than a viral expression element. The increased activity of the immunoglobulin enhancer element compared to a viral enhancer element as taught by Banerji et al. provides sufficient motivation for the skilled artisan to use the immunoglobulin enhancer over a viral enhancer. Furthermore, at the time of filing, B cells were well known to be professional antigen presenting cells. Thus, the large percentage of B cells, potent antigen presenting cells, in the spleen provides further motivation for utilizing a B cell specific expression element. As such, the fact that B cells were known at the time of filing to be professional antigen presenting cells, and that the spleen contains a large percentage of B cells, would provide the skilled artisan with a more than reasonable expectation that intrasplenic injection of the vector taught by Hurpin et al., modified to include the immunoglobulin enhancer element taught by Banerji et al., would result in transfection of B cells, the expression of the heterologous epitope in those cells, and the generation of immune responses.

Therefore, for reasons of record as discussed in detail above, the rejection of claims 3-4, 18-19, 29, 31, and 35 is maintained.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER